Introduction of Dissolution Profile
6.0 INTRODUCTION OF DISSOLUTION PROFILE

The History of Dissolution Testing

Let's look at the history of dissolution testing, starting from the beginning.

It all started in 1897 with the first reference to dissolution: Noyes and Whitney publish a paper on "The Rate of Solution of Solid Substances in Their Own Solution." They suggested that the dissolution rate was controlled by a layer of saturated solution that forms instantly around a solid particle.

A few years later in 1900, Brunner and Tolloczko proved that dissolution rate depended on the chemical, physical structures of the solid, the surface area exposed to the medium, agitation speed, medium temperature and the overall design of the dissolution apparatus.

1904-Nernst and Brunner modified the Noyes-Whitney equation by applying Fick's law of diffusion. A relationship between the dissolution rate and the diffusion coefficient was established.

1930-Experiments begin with in vivo-In vitro correlations.

1931-Hixon and Crowell develop the cube-root law of diffusion.

1934-Switzerland's Pharmacopeia Helvetica was the first regulatory body to introduce a disintegration test for tablets.

1950's-Emphasis moved from studying the effects of physiochemical properties of drugs on dissolution to correlation of dissolution to bioavailability of dosage forms.

1951-Edwards suggested that the analgesic activity of aspirin can be manipulated by its rate of dissolution within the GI tract.

1958-The rotating bottle method was developed to study extended release formulations.

1960's-Although it was recognized that disintegration was a critical process, deaggregation was essential for bioavailability. USP recognized a need for a standardized dissolution test. The USP began experimenting with a variety of basket and stirring devices.

1960-Levy and Hayes, utilizing a beaker and a three blade stirrer at 30-60 RPM, found significant differences in the in vitro dissolution rates of different brands of aspirin tablets and linked them to the incidence of gastrointestinal irritation caused by various brands due to their slow dissolution rates.

1970- USP 18 incorporated the first official dissolution test for solid dosage forms. Twelve Monographs published in USP-NF with the official dissolution test- a rotating basket.

1970's-Scientist find great variation in dissolution results from one apparatus to another. USP and FDA pushed for standardization of dissolution testing.

1975-USP begins development of calibrators for dissolution testing.

1978-FDA publishes “Guidelines for Dissolution Testing” (1)

USP proposes three calibrator tablets

Prednisone(disintegrating), Salicylic Acid (Non-disintegrating), Nitrofurantoin (disintegrating), but no predefined calibration frequency.

1990-Apparatus 3-Paddle over disk

Apparatus 4-Cylinder
Apparatus 5-Reciprocating Disk

1995-Apparatus 6-Cylinder

Apparatus 7- Reciprocating Disk (1)

1997-Pharmacia and Upjohn decided that it would no longer make USP Calibrator tablets

1997-USP Reformulated Prednisone tablets with the University of Maryland.

1997-USP extended upper range of Salicylic Acid.

1998-USP proposed reduction in chemical calibration and increase of mechanical calibration parameters.


**DRUG LEGISLATION**

The first legislation that mandated drug manufacturers to test their products for safety. This initiative was passed in the aftermath of the Elixir of Sulphanilamide tragedy which killed 107 people mostly infants in 1938. A pharmaceutical company in Tennessee marketed Sulphanilamide (a recently developed antibacterial drug) against strep throat infections for children as a syrup using diethylene glycol (antifreeze) as solvent. This solvent is lethal and this drug was never tested for safety. (The only way that the FDA was able to seize the drug was on the grounds that it was mislabelled; 'elixir' is defined as a product dissolved in alcohol.) The most important aspect of the law; - it forbade the sale of any drug unless the FDA found it to be safe.

1962: Proof of Efficacy: the Kefauver-Harris Act. An OTC sedative from Hoechst, thalidomide caused thousands of birth defects in Europe before it was banned. Although the tough FDA standards kept thalidomide from being sold here, some got out via free samples distributed to MDs.
In 1962 congress passed the first major amendment to the 1938 law, legislating that in addition to safety, the industry would now have to prove the effectiveness of drugs it was seeking to market.

1992 Accelerated FDA approval of drugs for life threatening or severely debilitating disease.

Dissolution test requirement :- General considerations

Generally compendia monographs incorporating dissolution test and specification for specific product provide a means to monitor batch-to-batch variability of these products. The two major aspect which decide the outcome of dissolution test are

(a) The type of dissolution test apparatus, and

(b) The dissolution test condition employed- e.g. Medium, composition, volume, speed, of rotating, temperature etc.

USP has enlisted different types of dissolution test apparatus along with their specification testing of a variety of formulation ranging form tablets to transdermal drug delivery system, which are as follows.
USP dissolution test apparatus.

<table>
<thead>
<tr>
<th>Apparatus</th>
<th>Descriptions</th>
<th>Formulation type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rotating basket</td>
<td>Floating dosage form capsules</td>
</tr>
<tr>
<td>2</td>
<td>Rotating paddle</td>
<td>Tablets</td>
</tr>
<tr>
<td>3</td>
<td>Reciprocating paddle</td>
<td>Bead type MR dosage forms</td>
</tr>
<tr>
<td>4</td>
<td>Flow-through cell</td>
<td>Formulation with limited solubility drugs</td>
</tr>
<tr>
<td>5</td>
<td>Paddle over disk</td>
<td>Transdermal dosage</td>
</tr>
<tr>
<td>6</td>
<td>Cylinder</td>
<td>Transdermal dosage</td>
</tr>
<tr>
<td>7</td>
<td>Reciprocating disk</td>
<td>Non disintegrating MR dosage forms.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Description</th>
<th>Pharmacopoeia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of media</td>
<td>500 – 1000ml</td>
<td>EIP, Ph, Eur</td>
</tr>
<tr>
<td>Ph</td>
<td>PH 1 - 6.8 water with justification</td>
<td>EIP, FDA</td>
</tr>
<tr>
<td></td>
<td>PH 1 - 7.6 water with justification</td>
<td>Ph, Eur</td>
</tr>
<tr>
<td>Additives</td>
<td>Enzymes, surfactants, salts</td>
<td>EIP</td>
</tr>
<tr>
<td></td>
<td>1% SLS Possible</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>Low concentration of surfactant</td>
<td>Ph, Eur</td>
</tr>
<tr>
<td>Deaeration</td>
<td>Product – by product Validation</td>
<td>EIP</td>
</tr>
<tr>
<td></td>
<td>Mandatory for flow through apparatus</td>
<td>Ph, Eur</td>
</tr>
</tbody>
</table>
Once the dissolution apparatus and test condition are selected, one has to set the criteria of drug release, dissolution test specification form a particular formulation under test, as the quality parameters, based on the number of specifications, the dissolution test can be referred as

(a) single–point, dissolution test (one dissolution specification) or

(b) multi-point dissolution test (more than one dissolution specification)

**Single point dissolution testing:**

In case of single-point dissolution testing amount of drug released at a particular time point is determined and specification for that time (e.g. NLT 85% in 15 min) decides the acceptable or unacceptable release behavior of the formulation.

Such a test is frequently recommended Q.C test for IR oral solid dosage forms. However, it is applicable only for Q.C. test of a highly soluble and rapidly dissolution drug products and can be considered adequate for biowaiver for rapidly dissolving products containing highly soluble and highly permeable drugs.

**Multi-point dissolution test:**

Characterization of complete dissolution profile:

In case of multi-point dissolution studies, release of a drug is monitored as a function of time. i.e amount of drug released at more than one time points is monitored.

Multi-point dissolution study is also termed as dissolution profile study. The specification for release at different time points characterize the release behavior of the formulation throughout
the course of dissolution testing such test and their specifications are applicable in following cases-

➤ For establishing quality of MR products.
➤ To define in vitro dissolution specification for generic IR or MR product.
➤ To waive bioequivalence requirement for lower strengths of an IR dosage form.
➤ To establish IR products sameness after certain changes in components and composition. (except for drugs with high solubility and high permeability ), in batch size and in manufacturing equipment.
➤ In developing point-to-point correlations or predictting the entire in vivo plasma profile based on dissolution data, regardless the type of the product.

**Biopharmaceautics classification system**

Classification of drugs based on their biopharmaceutical properties.

It has been established that the bioavailability rate and extend of absorption of a drug offer Oral administration depends of a drug offer oral administration depends on two Fundamental factor – (1) drug dissolution and (2) permeability of the drug through GIT. Biopharmaceutics classification system (BCS) and likelihood of IVIVC for IR formulations. Class solubility permeability IVIVC expectations.

**DISSOLUTION**

Apparatus 1: A rotating mesh (40 mesh standard) basket in a hemispherical vessel.

Apparatus 2: A rotating paddle in a hemispherical vessel.

Apparatus 3: A reciprocating cylinder in a cylindrical vessel.
Apparatus 4: A media flow through cell.

Apparatus 5: A rotating paddle over a disk in a hemispherical vessel.

Apparatus 6: A rotating cylinder in a hemispherical vessel.

Apparatus 7: A reciprocating holder in a cylindrical vessel. (disk, cylinder, pointed rod, spring holder, angled disk)

Batch: A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits (21 CFR 210.3(b)(2)).

Batch formula (composition): A complete list of the ingredients and their amounts to be used for the manufacture of a representative batch of the drug product. All ingredients should be included in the batch formula whether or not they remain in the finished product (Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products, FDA February 1987).

Bioavailability: The rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action (21 CFR 320.1(a)).

Bio batch: A lot of drug product formulated for purposes of pharmacokinetic evaluation in a bioavailability/bioequivalence study. This lot should be 10% or greater than the proposed commercial production batch or at least 100,000 units, whichever is greater.

Bioequivalent drug products: Pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or
multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labelling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied (21 CFR 320.1(e)).

Biopharmaceutics classification system: a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as follows (2).

Class 1: High Solubility - High Permeability

Class 2: Low Solubility - High Permeability

Class 3: High Solubility - Low Permeability

Class 4: Low Solubility - Low Permeability

In addition, IR solid oral dosage forms are categorized as having rapid or slow dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool to help sponsors justify requests for biowaiver.

CR: Controlled release (3).

Convolution: Prediction of plasma drug concentrations using a mathematical model based on the convolution integral.
Correlation: As used in this guidance, a relationship between in vitro dissolution rate and in vivo input (absorption) rate. 21

Deaggregation: The state in which small aggregates are no longer intact.

Deconvolution: Estimation of the time course of drug input (usually in vivo absorption or dissolution) using a mathematical model based on the convolution integral.

Development: Establishing an in vitro/in vivo correlation. Drug product: A finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)).

Disintegration: The state in which the dose form is no longer intact except for small aggregates.

Disintegration test: USP <701>.

DR: Delayed release.

ER: Extended release.

Extended release dosage form: A dosage form that allows a reduction in dosing frequency as compared to that presented by a conventional dosage form, e.g., a solution or an immediate release dosage form.

Evaluation: In the context of in vitro/in vivo correlation, a broad term encompassing experimental and statistical techniques used during development and evaluation of a correlation which aid in determining the predictability of the correlation.

F2: A similarity factor used to compare multipoint dissolution profiles.

Formulation: A listing of the ingredients and composition of the dosage form. In vitro/in vivo correlation: A predictive mathematical model describing the relationship between an in vitro property of an extended release dosage form (usually the rate or extent of drug dissolution or
release) and a relevant in vivo response, e.g., plasma drug concentration or amount of drug absorbed.


In vivo release: In vivo dissolution of drug from a dosage form as determined by deconvolution of data obtained from pharmacokinetic studies in humans (patients or healthy volunteers).

Level A correlation: A predictive mathematical model for the relationship between the entire in vitro dissolution/release time course and the entire in vivo response time course, e.g., the time course of plasma drug concentration or amount of drug absorbed.

Level B correlation: A predictive mathematical model for the relationship between summary parameters that characterize the in vitro and in vivo time courses, e.g., models that relate the mean in vitro dissolution time to the mean in vivo dissolution time, the mean in vitro dissolution MDT vitro \( \int_0^4 (M 4 & M (t)) dt \) M 4 23 time to the mean residence time in vivo, or the in vitro dissolution rate constant to the absorption rate constant.

Level C correlation: A predictive mathematical model of the relationship between the amount dissolved in vitro at a particular time (or the time required for in vitro dissolution of a fixed percent of the dose, e.g., T %) and a summary parameter that characterizes the in vivo time 50 course (e.g., C or AUC). Max.

Lot: A batch, or a specific identified portion of a batch, having uniform character and quality within specified limits or, in the case of a drug product produced by continuous process, a
specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits (21 CFR 210.3(b) (10)).

Mean absorption time: The mean time required for drug to reach systemic circulation from the time of drug administration. This term commonly refers to the mean time involved in the in vivo release and absorption processes as they occur in the input compartment and is estimated as \( \text{MAT} = \text{MRT} - \text{MRT oral i.v.} \)

Mean in vitro dissolution time: The mean time for the drug to dissolve under in vitro dissolution conditions.

Mean residence time: The mean time that the drug resides in the body. MRT may also be the mean transit time. \( \text{MRT} = \text{AUMC/AUC} \). Narrow therapeutic index drugs: Drugs having, for example, less than a two-fold difference in the minimum toxic concentrations and the minimum effective concentrations (21 CFR 320.33 (c)).

MR: Modified release.

Non release controlling excipients (noncritical compositional variable): An inactive ingredient in the final dosage form that does not significantly affect the release of the active drug substance.

Occluded: Drug substance that is not collected or analyzed due to adsorption, absorption, and containment in the dosage form.

Occlusion: The point in a dissolution profile in which drug substance not longer is released into the media.

Occultation: The point in a dissolution profile in which drug substance release rate is slowing to the occlusion point.
PR: Prolonged release.

Predictability: Verification of the model's ability to describe in vivo bioavailability results from a test set of in vitro data (external predictability) as well as from the data that was used to develop the correlation (internal predictability).

Percent prediction error: \[
\%PE = \left(\frac{\text{Observed value} - \text{Predicted value}}{\text{Observed value}}\right) \times 100
\]

Release controlling excipients (critical compositional variable): An inactive ingredient in the final dosage form that functions primarily to extend the release of the active drug substance from the dosage form.

Release mechanism: The process by which the drug substance is released from the dosage form.

Release rate: Amount of drug released per unit of time as defined by in vitro or in vivo testing.

Statistical moments: Parameters that describe the characteristics of the time courses of plasma concentration (area, mean residence time, and variance of mean residence time) and of urinary excretion rate.

SR: Sustained release.


Dissolution Discussion Group, Volume 1, A user's perspective on Dissolution.

Guidance for Industry. Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification
An Introduction to Drug Release Theory

Drug Absorption from a solid oral dosage depends on the release of the drug substance from the drug product (dissolution), the solubility, and the permeability across the gastrointestinal tract. The first aspect of the tablets is determined by the manufacture of the product. The next two aspects are determined by the properties of the active pharmaceutical. All solid oral dosage forms can be characterized according to these three properties.

Dissolution Profiling

Dissolution profile of two products (12 units each) of the test and reference products.

To use the mean dissolution values from both curves, the percent coefficient of variation at the earlier time points should not be more than 20% and at other time points should not be more than 10%. Only one measurement should be considered after 85% dissolution of both of the products.

The dissolution measurements of the test and reference batches should be made under exactly the same conditions.

Dissolution & Particle Size

In order for a drug to have its effect after oral administration it must go into solution and then diffuse through the gut wall into the body. The first step in that process is the disintegration of the dosage form followed by dissolution of the active ingredient. Dissolution of a pure substance follows the Noyes Whitney Equation. $\frac{dc}{dt} = kS(Cs - Ct)$ where $\frac{dc}{dt}$ is the rate of dissolution, $k$ is the dissolution rate constant, $S$ is the surface area of the dissolving solid, $Cs$ is the saturation concentration of drug in the diffusion layer and $Ct$ is the concentration of drug in dissolution.
media (or the bulk). One way to increase dissolution rate of poorly soluble drugs is to increase the surface available for dissolution. This is done by reducing particle size or by dividing the dosage form into two smaller tablets or capsules, with a larger combined surface area. Other ways include increasing the disintegration rate and deaggregation.

**Dissolution:**

- Dissolution is a process in which a solid substance solubilizes in a given solvent i.e., mass transfer from the solid surface to the liquid phase.
- OR Dissolution is the process by which a solid substance dissolves. It is controlled by the affinity between the solid and the medium.
- Following points should be considered when dosage form undergoes dissolution.

Physical characteristics of dosage form, wettability, penetration ability of dissolution medium, swelling process, disintegration of dosage unit (4).

- For dissolution following scheme may be proposed.

Tablet or capsule $\longrightarrow$ Granules $\longrightarrow$ Fine particles

\[ \downarrow \]  \[ \checkmark \text{Disintegrate and dissolve} \]

Drug in solution

\[ \downarrow \]

Drug in blood
Definition of IVIVC

- It has been defined by food and drug administration as “a predictive mathematical model describing the relation between an in-vitro property of a dosage form and an in-vivo response”
- In vitro property is the rate of extent of drug dissolution or release while the in-vivo response is the plasma drug concentration or amount of the drug absorbed.
- The United States Pharmacopoeia (USP) also defines IVIVC as “the establishment of a relationship between a biological property, or a parameter derived from a biological property produced from a dosage form, and a physicochemical property of the same dosage form”.
- The parameter derived from the biological property is AUC or Cmax, while the physicochemical property is the in vitro dissolution profile.
- The main objective of developing and evaluating an IVIVC is to establish the dissolution test as surrogate for human bioequivalence studies which may reduce the number of bioequivalence studies performed during the initial approval process as well as with certain scale up and post approval changes.

Importance of IVIVC:

- Serves as a surrogate of in vivo and assist in supporting biowaiver.
- Support and / or validates the use of dissolution methods and a specifications
- Assist in quality control during manufacturing and selecting appropriate formulations.
- It is also used as quality control for product performance. But this quality control may sometime be more rigorous than the usual control standards since it depends on the product bioavailability.
Helps to minimize the number of bioequivalence studies performed during the initial approval process and during the scaling up and post approval changes.

It minimizes the time and cost invested in additional bioavailability studies. The general dissolution time point specification is ±10% deviations from the mean dissolution profile obtained from the bio batch. The bio equivalency between formulations would be expected if the formulation(s) fall within the upper and lower limits of the specification.

Levels of the IVIVC

There are four level of the IVIVC that has been described in the FDA guidance, which include level A, B, C, AND MULTIPLE C.

Level A correlation:

- This correlation represents a point to point relationship between in vitro dissolution and in vivo dissolution (input/absorption rate).
- It is also viewed as a predictive model for the relationship between the entire in vitro release time course and entire in vivo response time course.
- Correlation is linear at this level.
- It is the most informative and very useful from a regulatory perspective.

Level B correlation:

- The mean in vivo dissolution or mean residence time is compared to the mean Invitro dissolution time by using statistical moment analytical methods.
- This type of correlation uses all of the In vitro and in vivo data; thus it is not considered as a point to point correlation.
This is of limited interest and use because more than one kind of plasma curve produces similar mean residence time.

**Level C correlation:**

- It describes a relationship between the amount of drug dissolved (% drug dissolved at 1 hour) at one time point and one pharmacokinetic parameter (e.g., either AUC or Cmax).
- It is considered as the lowest correlation level as it doesn't reflect the complete shape of the plasma concentration time curve.

**Multiple level C correlation:** relates one or more pharmacokinetic parameters to the percent drug dissolved at several time points of the dissolution profile and thus may be more useful.

- Level B and level C correlation can be useful in early formulation development, including selecting the appropriate excipients, to optimize manufacturing processes, for quality control purpose, and to characterize the release patterns of newly formulated immediate release and modified release products relative to the reference.

**Roll of BCS as an indicator of developing an IVIVC:**

- It is a fundamental guideline for determining the conditions under which the ivivc are expected.
- It is also used as a tool for developing the in vitro dissolution specification.
- The classification is associated with drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers: the absorption number, the dissolution number and the dose number.
  1. **Absorption number:** is the ratio of the mean residence time to the absorption time.
  2. **Dissolution number:** is the ratio of mean residence time to mean dissolution time.
(3) **Dose number:** is the mass divided by an uptake volume of 250 ml and the drug's solubility.

(4) **Mean residence time:** is the average of the residence time in the stomach, small intestine and the colon.

(5) The fraction of dose absorbed then can be predicted based on these three parameters. For example, absorption number 10 means that the permeation across the intestinal membrane is 10 times faster than the transit through the small intestine indicating 100% drug absorbed.

The drug is classified based on solubility and intestinal permeability.

**BCS and expected ivivc for immediate release drug products.**

<table>
<thead>
<tr>
<th>Class</th>
<th>Solubility</th>
<th>Permeability</th>
<th>IVIVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High</td>
<td>High</td>
<td>Correlation (if dissolution is rate limiting step)</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>High</td>
<td>IVIVC expected</td>
</tr>
<tr>
<td>3</td>
<td>High</td>
<td>Low</td>
<td>Little or no IVIVC</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>Low</td>
<td>Little or no IVIVC</td>
</tr>
</tbody>
</table>
**BCS for extended release drug products.**

<table>
<thead>
<tr>
<th>CLASS</th>
<th>S</th>
<th>P</th>
<th>IVIVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>High and site independent</td>
<td>High and site independent</td>
<td>IVIVC level A expected</td>
</tr>
<tr>
<td>IB</td>
<td>High and site independent</td>
<td>Dependant on site and narrow absorption window</td>
<td>IVIVC level C expected</td>
</tr>
<tr>
<td>IIA</td>
<td>Low and site independent</td>
<td>High and site independent</td>
<td>IVIVC level A expected</td>
</tr>
<tr>
<td>IIB</td>
<td>Low and site independent</td>
<td>Dependant on site and narrow absorption window</td>
<td>Little or no IVIVC</td>
</tr>
<tr>
<td>Va:acidic</td>
<td>variable</td>
<td>Variable</td>
<td>Little or no IVIVC</td>
</tr>
<tr>
<td>Vb:basic</td>
<td>variable</td>
<td>Variable</td>
<td>IVIVC level A expected</td>
</tr>
</tbody>
</table>

**Development of IVIVC**

**IVIVC Model Development**

- Development of an IVIVC consists of model development and model validation.
- A number of methods are available to probe the in vitro-in vivo relationships.
- Among the earliest methods are the two-stage Deconvolution methods that involve estimation of the in vivo absorption profile from the concentration-time data using the Wagner-Nelson or Loo-Riegelman methods (Stage 1). Subsequent to the estimation of the in vivo absorption profile, the relationship with in vitro dissolution is evaluated (Stage 2).
More recently, one-stage convolution-based approaches for IVIVC have been investigated. The one-stage convolution methods compute the in vivo absorption and simultaneously model the in vitro-in vivo data.

While the two-stage method allows for systematic model development, the one-stage method obviates the need for the administration of an intravenous, oral solution or immediate-release bolus dose.

The most basic IVIVC models are expressed as a simple linear equation (Equation 1) between the in vivo drug absorption and in vitro drug dissolved (released).

**Equation 1.**

\[ Y \ (\text{in vivo absorbed}) = m \times X \ (\text{in vitro drug dissolved}) + C \]

In this equation, \( m \) is the slope of the relationship, and \( C \) is the intercept. Ideally, \( m=1 \) and \( C=0 \), indicating a linear relationship.

However, depending on the nature of the modified-release system, some data are better fitted using nonlinear models, such as Sigmoid, Weibull, Higuchi, or Hixson-Crowell.

Equation 1 may be applied to most formulations with comparable in vitro and in vivo duration of release. However, for dosage forms with complicated mechanisms of release, which are of longer duration, in vitro release may not be in the same time scale as the in vivo release.
Thus, in order to model such data, it is necessary to incorporate time-shifting and time-scaling parameters within the model (Figure 1). This is the kind of data that is routinely encountered in the development of sustained-release dosage forms.

In vivo release rate ($X'_{vivo}$) can also be expressed as a function of in vitro release rate ($X'_{rel,vitro}$) with parameters ($a$, $b$), which may be empirically selected and refined using appropriate mathematical processes as shown in Equation 2. An iterative process may be used to compute the time-scaling and time-shifting parameters.

$$X'_{vivo} (t) = X'_{rel,vitro} (a+bt)$$

**IVIVC Model Validation**

- The objective of any mathematical predictive tool is to successfully predict the outcome (in vivo profile) with a given model and test condition (in vitro profile).

- Integral to the model development exercise is model validation, which can be accomplished using data from the formulations used to build the model (internal validation) or using data obtained from a different (new) formulation (external validation).

- While internal validation serves the purpose of providing basis for the acceptability of the model, external validation is superior and affords greater "confidence" in the model.
Internal Validation: Using the IVIVC model, for each formulation, the relevant exposure parameters ($C_{\text{max}}$ and AUC) are predicted and compared to the actual (observed) values. The prediction errors are calculated using Equation 3.

\[
\text{Prediction Error (\%PE) = } \left( \frac{C_{\text{max\ observed}} - C_{\text{max\ predicted}}}{C_{\text{max\ observed}}} \right) \times 100 \quad \text{or} \quad \left( \frac{\text{AUC}_{\text{observed}} - \text{AUC}_{\text{predicted}}}{\text{AUC}_{\text{observed}}} \right) \times 100
\]

The criteria set in the FDA guidance on IVIVC are as follows: For $C_{\text{max}}$ and AUC, the mean absolute percent prediction error (% PE) should not exceed 10%, and the prediction error for individual formulations should not exceed 15%.

External Validation:

- For establishing external predictability, the exposure parameters for a new formulation are predicted using its in vitro dissolution profile and the IVIVC model, and the predicted parameters are compared to the observed parameters.
- The prediction errors are computed as for the internal validation. For $C_{\text{max}}$ and AUC, the prediction error for the external validation formulation should not exceed 10%.
- A prediction error of 10% to 20% indicates inconclusive predictability and illustrates the need for further study using additional data sets.
- For drugs with narrow therapeutic index, external validation is required despite acceptable internal validation, whereas internal validation is usually sufficient with non-narrow therapeutic index.
(1) **Establishment of the dissolution system for IVIVC**

- The dissolution is proposed to be a **surrogate of drug bioavailability**. Thus more rigorous dissolution standard may be necessary for the in vivo waiver.

- A dissolution methodology which is able to discriminate between the study formulations and which best reflects the in vivo behavior would be selected.

Are specified by the USP and recommended in the FDA guidance especially for modified release dosage form.

- Other methodologies may be used however the first four are preferred, especially the **basket and paddle**. It is also recommended to start with the basket or paddle method prior to using others.

- The in vitro dissolution release can be modified to facilitate the correlation development.

- Changing dissolution conditions such as the **stirring speed, choice of apparatus, pH of medium, and temperature may alter the dissolution profile**.

- Dissolution testing conditions should be selected so that the formulation behaves in the same manner as the in vivo dissolution.

- The appropriate dissolution testing should also discriminate between different formulations that possess different release patterns.

- A common **dissolution medium** is water, simulated gastric fluid (pH 1.2), or intestinal fluid (ph 6.8 or 7.4) without enzyme, and buffers with a pH range of 4.5 to 7.5.
Biorelevant dissolution media:

<table>
<thead>
<tr>
<th>Fasted state simulated intestinal fluids</th>
<th>Fed state simulated intestinal fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PH</strong></td>
<td><strong>PH</strong></td>
</tr>
<tr>
<td>6.8</td>
<td>6.5</td>
</tr>
<tr>
<td>280-310+10 Osmolality (mOsmol)</td>
<td>270-10 Osmolality(mOsmol) 635-10</td>
</tr>
<tr>
<td>Na Taurocholate 5mM</td>
<td>Na Taurocholate 15mM</td>
</tr>
<tr>
<td>Lecithin 1.5mM,3.75mM</td>
<td>Lecithin 3.75mM</td>
</tr>
<tr>
<td>KH2PO4 .029mM 3.9g</td>
<td>Acetic acid 8.65g</td>
</tr>
<tr>
<td>KCl .22M 7.7g</td>
<td>KCl 15.2g</td>
</tr>
<tr>
<td>NaOH Qs pH 6.8</td>
<td>NaOH Qs pH 5.0</td>
</tr>
<tr>
<td>Deionizer Water Qs 1 liter</td>
<td>Deionizer Water Qs 1 liter</td>
</tr>
</tbody>
</table>

Fasted state simulated gastric fluid

<table>
<thead>
<tr>
<th>HCl</th>
<th>.001-.005 N6.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na Lauryl sulfate</td>
<td>2.5g</td>
</tr>
<tr>
<td>NaCl</td>
<td>2g</td>
</tr>
<tr>
<td>Distilled water</td>
<td>Qs 1 liter</td>
</tr>
</tbody>
</table>

- For sparingly soluble drugs, use of surfactant in the dissolution medium is recommended.
- A simple aqueous dissolution media also recommended for BCS class 1 drug as this type of drug exhibit lack of influence of the dissolution medium properties.
- Water and simulated gastric fluid then are the default mediums for most of the class 1 drugs. A typical medium volume is 500 to 1000 ml.
The normal test duration for immediate release is 15 to 60 minutes with a single time point. For example class 1 recommended 15 minutes.

Additionally two time points may be required for the BCS class 2 at 15 minutes and the other time at which 85% of the drug is dissolved.

In vitro dissolution tests for a modified release dosage form require at least 3 time points to characterize the drug release.

The first sampling time (1-2 hours or 20-30% release) is chosen to check dose dumping potential. The intermediate time point has to be around 50% drug release in order to define the in vitro release profile.

The last point is to define essentially complete drug release. The dissolution limit should be at least 80% of drug release. Further justification as well as 24 hrs test duration are required if the percent drug release is less than 80.

Once the discriminatory system is established, dissolution conditions should be fixed for all formulations tested for development of the correlation.

A dissolution profile of percentage or fraction of drug dissolved versus time then can be determined.

11. TECHNIQUES OF IN VIVO DISSOLUTION

11.1 Calculation of parameters

In vivo dissolution measurement

(% Absorbed time plot)

The techniques available for evaluation in vivo dissolution rate could be divided into two categories:
ANALYSIS OF HETEROCYCLIC DRUGS

➢ Direct method and

➢ Indirect method

Indirect methods:

(1) Wagner-Nelson method (one compartment model)

(2) Loo – Riegleman analysis (multi compartment model)

(3) Statistical moment

(4) Deconvolution method

(1) Wagner – Nelson method

➢ Used for one compartment model.

➢ The amount of drug that has been absorbed into the systemic circulation \( X_a \), at any time after administration will equal the sum of the amount of drug in the body \( X \), and the cumulative amount of drug eliminated, \( X_e \) by urinary excretion, by metabolism and by all other routes at that time. Thus,

\[
X_a = X + X_e \quad \text{ .................. (1)}
\]

Which when differentiated with respect to time becomes,

\[
dX_a/dt = dX/dt + dXe/dt \quad \text{ .................. (2)}
\]

The term \( dXe/dt \) is by definition equal to the product of the amount of drug in the body \( X \) and apparent first-order elimination rate constant of drug from the body;

\[
dXe/dt = k \times X \quad \text{ ....... (3)}
\]

Substitution of \( kX \) for \( dXe/dt \) in equation ...... (2) Yields.

\[
dXa/dt = dX/dt + kX \quad \text{ ....... (4)}
\]
since \( X = V \times C \)

\( V = \) apparent volume of distribution

\( C = \) plasma concentration of drug

\[
\frac{dX_a}{dt} = V \times C + k \times V \times C \quad \cdots \cdots \quad (5)
\]

Integration of equation (4) from time zero to \( T \) yields the following expression for the amount of drug absorbed to time \( T \), \((X_a)_T\)

\[
(X_a)_T = V \times \Theta_T + k \times V \times \int_0^T C \, dt \quad \cdots \cdots \quad (6)
\]

\( \Theta_T = \) plasma concentration of drug at time \( T \)

\( \int_0^T C = \) AUC of plasma concentration to time

An equation for the amount of the drug ultimately absorbed, \((X_a)_{\text{inf}}\), can be obtained by integrating equation \((5)\) from time zero to infinity and recognizing \( C \) equal zero at both times zero and infinity. Thus,

\[
(X_a)_{\text{inf}} = k \times V \times \int_0^\infty C \, dt \quad \cdots \cdots \quad (7)
\]

where \( \int_0^\infty C \, dt = \) total AUC

Dividing (6) and (7) and canceling common terms yields the expression for the fraction absorbed to time \( T \).

\[
\frac{(X_a)}{(X_a)_{\text{inf}}} = \frac{\Theta_T + k \times \int_0^T C \, dt}{k \times \int_0^\infty C \, dt} \quad \cdots \cdots \quad (8)
\]

Equation (8) relates the cumulative amount of drug absorbed after a certain time or the amount of drug ultimately absorbed rather than to the dose administered. By collecting blood after single

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oral dose and determining drug concentration in plasma and the elimination rate constant, one can calculate the fraction absorbed for various times after administration.

Urinary data can also be employed to construct % absorbed-time plots. The excretion rate of intact drug in the urine $dX_u/dt$ is given by

$$DX_u/dt = ke \times X...............(9)$$

Same as above calculation, one can estimate % absorbed at time $T$.

$$X_a)T/(X_a)inf = (dX_u/dt) + k \times (X_u)T / k \times (X_u)inf$$

**Limitation**

- It applies rigorously only to Wagner-Nelson method (One compartment characteristics).
- When drug concentration time curve after oral administration of the drug shows multi-compartment characteristic and on i.v. injection suggest one compartment model. analysis of those data produce incorrect result.

**FACTORS AFFECTING CORRELATION :-**

Factors considering while correlation dissolution and BA.

(1) Blood flow and drug permeability

(2) Food and fluid volume

(3) Drug metabolism and intestinal mucosa
(4) Metabolic activity of intestinal micro flora

1. Blood flow and drug permeability:

2. Rate limiting step in drug absorption are blood flow or drug permeation through the membrane.

3. eg. Treated water moves freely through aq. Pores.

4. Ribitol absorption is controlled by diffusion through the membrane
   a. Urea is compound with intermediate permeability characteristic.

2 Food and fluid volume:

Drug absorption may be reduced increased of unaffected in the presence of food.

<table>
<thead>
<tr>
<th>REDUCED</th>
<th>DELAYED</th>
<th>INCREASED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>cephalosporin</td>
<td>Chlorothiazide</td>
</tr>
<tr>
<td>Aspirin</td>
<td>diclofenac</td>
<td>griseofulvin</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Digoxin</td>
<td>Riboflavin</td>
</tr>
</tbody>
</table>

3. Drug metabolism and intestinal mucosa:

Salicylamide and A.A completely inhibit the intestinal mucosa metabolism of Isoprenaline. Drug reaching the intestinal tract normally be inactive by metabolism to the sulphate conjugate but co-administrating of drug competing for ingestion enzyme would result in a potentiation of p'cological activity.

4. Metabolic activity of intestinal micro flora:
   a. Principal organisms appears to be anaerobic and bifid bacteria which are found in colon, stomach and jejunum.
i. Inactivation of Digoxin by reduction of the lactone by anaerobic bacteria.

Dissolution Test Apparatus

DELAYED-RELEASED (ENTERIC-COATED) ARTICLES – GENERAL DRUG RELEASE STANDARD

Method A or Method B

Method A

Procedure  **Acid stage**

- Place 750 ml of 0.1N HCl acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37±5°. Place 1 tab / cap. In the apparatus, cover the vessel, and operate the apparatus for 2 hr. at rate specified in the monograph. After 2 hr. of operation in 0.1N HCL acid, withdraw an aliquot of the fluid & perform an analysis, and proceed immediately as directed for buffer stage.

- The requirement of this portion of the test is met if the quantities, based on the percentage of the labeled content of active ingredient dissolved from the units conform to acceptance table 2.

- **Acceptance Table 2.**

<table>
<thead>
<tr>
<th>level</th>
<th>No. Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁</td>
<td>6</td>
<td>No individual value exceed 10% dissolved</td>
</tr>
<tr>
<td>A₂</td>
<td>6</td>
<td>Average of the 12 units (A₁ + A₂) is not more than 10% dissolved, &amp; no individual unit is greater than 25% dissolved.</td>
</tr>
<tr>
<td>A₃</td>
<td>12</td>
<td>Average of the 24 units (A₁ + A₂ + A₃) is not more than 10% dissolved, &amp; no individual unit is greater than 25% dissolved.</td>
</tr>
</tbody>
</table>

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2. Buffer stage

- With the apparatus operating at the rate specified in the monograph, add to the fluid in the vessel 250 ml of 0.20 M tri basic sodium phosphate that has been equilibrated to 37 ± 0.5°.

- Adjust, if necessary, with 2N HCl acid / 2N NaOH to a pH of 6.8±0.05. Continue to operate the apparatus for 45 min. or for the time specified in the individual monograph.

- At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis.

Interpretation

- The requirements are met if the quantities of active ingredient dissolved from the units tested conform to acceptance table 3. Continue testing through the three levels unless the results of both stages conform at earlier level. The value of Q in acceptance table 3 is 75% dissolved unless otherwise specified in the individual monograph. The quantity Q, specified in the individual monograph, is the total amount of active ingredient dissolved in both the acid and buffer stages, expressed as a % of the labeled content. The 5% & 15% values in acceptance table 3 are % of the labeled content so that these values and Q are in the same terms.

Acceptance Table 3

<table>
<thead>
<tr>
<th>level</th>
<th>No. Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>B₁</td>
<td>6</td>
<td>Each unit is not less than Q+5%.</td>
</tr>
<tr>
<td>B₂</td>
<td>6</td>
<td>Average of 12 units (B₁+B₂) is equal to or greater than Q and no unit is less than Q-15%.</td>
</tr>
<tr>
<td>B₃</td>
<td>12</td>
<td>Average of 24 units (B₁+B₂+B₃) is equal to or greater than Q, and not more than 2 units are less than Q-15%, and no unit is less than Q-25%.</td>
</tr>
</tbody>
</table>
Apparatus 3 (Reciprocating cylinder)

Apparatus

➢ The assembly consists of set of cylindrical, flat-bottomed glass vessels, a set of glass reciprocating cylinders, stainless steel fittings and screens, motors, drive assembly to reciprocate the cylinder vertically inside the vessels and, if desired, index the reciprocating cylinders horizontally to a different row of vessels.

➢ The vessels are partially immersed in a suitable water bath of any convenient size that permits holding the temperature at 37±0.5° during the test.

➢ A device is used that allow the reciprocating rate to be selected and maintained at the dip rate specified in the individual monograph, within ± 5%.
Dissolution Medium

- Use the solvent specified in the individual monograph. If the dissolution medium is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the pH specified in the individual monograph.

Procedure

- Place the stated volume of the dissolution medium in each vessel of the apparatus, assemble the apparatus, equilibrate the dissolution medium to 37±0.5°, and remove the thermometer.
- Place the 1 dosage form unit in each of the six reciprocating cylinder, taking care to exclude air bubbles from the surface of each of the dosage unit, and immediately operate the apparatus as specified in the individual monograph during the upward and downward stroke, the reciprocating cylinder moves through a total distance of 9.9 to 10.1 cm.
- Within the time interval is specified, or at each of the times stated, raised the reciprocating cylinder and withdraw a portion of the solution under test from a zone midway between the surface of the dissolution medium and the bottom of each vessel.
- Perform the analysis as directed in the individual monograph.
- If necessary, repeat the test with additional dosage units.
- Where capsule shell interfere with the analysis, remove the content of not fewer than 6 capsule as completely as possible, and dissolve the empty capsule shell in the specified volume of the dissolution medium.
- Perform the analysis as directed in the individual monograph.
- Make any necessary correction. Correction factor greater than 25% of the labeled content is unacceptable.
**Time**

- The test-time point, generally three are expressed in hr. specimens are to be withdrawn within a tolerance of ±2% of the stated time.

**Interpretation**

- unless otherwise specified in the individual monograph, the requirement are met if the quantities of active ingredient dissolved from the units tested conform to acceptance Table 1 . continue testing through the three levels unless the results conform at either L1 or L2 . limit on the amount of active ingredient dissolved are in terms of the percentage of labeled content. Limits embrace each value of Qt , the amount dissolved at each specified fractional dosing interval. Where more than one range is specified in the individual monograph, the acceptance criteria apply individually to each range.

**Acceptance Table 1**

<table>
<thead>
<tr>
<th>Level</th>
<th>No. Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>6</td>
<td>No individual value lies outside each of the stated range and, no individual value is less than the stated amount at the final test time.</td>
</tr>
<tr>
<td>L2</td>
<td>6</td>
<td>The average value of the 12 units (L1 + L2) lies within each of the stated range and is not less than the stated amount at the final test time, none is more than 10% of labeled content outside each of the stated ranges, and none is more than 10% of labeled content below the stated amount at the final test time.</td>
</tr>
<tr>
<td>L3</td>
<td>12</td>
<td>The average value of the 24 units (L1 + L2 + L3) lies within each of the stated ranges, and is not less than the stated amount at the final test time, not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated range, not more than 10% of labeled content below the stated amount at the final test time and none of the units is more than 20% of labeled content outside each of the stated range or more than 20% of labeled content below the stated amount at the final test time.</td>
</tr>
</tbody>
</table>
Apparatus 4 (Flow-Through cell)

Apparatus

➢ The assembly consists of a reservoir and a pump for the dissolution medium, a flow-through cell, a water bath that maintains the dissolution medium at 37±0.5°. The cell size is specified in the individual monograph.

Procedure

➢ Place the glass beads into the cell specified in the monograph. Place 1 dosage form unit on top of the beads or, if specified in the monograph, on a wire carrier.

➢ Assemble the filter head and fix rate specified in the individual monograph and measured with an accuracy of 5%.

➢ Collect the elute by fraction at each of the times stated. Perform the analysis as directed in the individual monograph.

➢ Repeat the test with additional dosage-form units.

Time & Interpretation

➢ Same as Apparatus 3
TRANSDERMAL DELIVERY SYSTEMS – GENERAL DRUG RELEASE STANDARDS

Apparatus 5 (Paddle over Disk)

Apparatus

➤ Use the paddle and vessel assembly from Apparatus 2 as described under Dissolution, with the addition of stainless steel disk assembly designed for holding the Transdermal system at the bottom of the vessel. The temperature is maintained at 32±0.5°C. A distance of 25±2mm between the paddle blade and the surface of the assembly is maintained during the test.

➤ The disk assembly for holding the transdermal system is designed to minimize any "dead" volume between the disk assembly and the bottom of the vessel. The disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade (Fig. 4).

Time

➤ The test time points, generally three, are expressed in hr. Specimens are to be withdrawn within a tolerance of ±15 min. or ±2% of the stated time.
**Interpretation**

Unless otherwise specified in the individual monograph, the requirement are met if the quantities ingredient released from the system conform to Acceptance table 4 for trance dermal drug delivery systems. Continue testing through the three levels unless the results conform at either $L_1$ or $L_2$.

**Acceptance table 4**

<table>
<thead>
<tr>
<th>level</th>
<th>No. Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L_1$</td>
<td>6</td>
<td>No individual values lies outside the stated range.</td>
</tr>
<tr>
<td>$L_2$</td>
<td>6</td>
<td>The average value of 12 units ($L_1+L_2$) lies within the stated range. No individual value is outside the stated by more than 10% of the average of the stated range.</td>
</tr>
<tr>
<td>$L_3$</td>
<td>12</td>
<td>The average value of 24 units ($L_1+L_2+L_3$) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average of the stated range, and none of the units is outside the stated range by more than 20% of the average of the stated range.</td>
</tr>
</tbody>
</table>

**Apparatus 6 (Cylinder)**

Apparatus Use the vessel assembly from *Apparatus 1*, except the basket and shaft with a stainless steel cylinder stirring element and to maintain the temperature at $32\pm 0.5^\circ$ during the test. The shaft and cylinder components of the stirring element are fabricated of stainless steel to the specifications shown in Fig.5. The dosage unit is placed on the
cylinder at beginning of each test. The distance between the inside bottom of the vessels and the cylinder is maintained at 25±2mm during the test.

**Time**

Same as Apparatus 5.

**Interpretation**

- Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to acceptance table 4 for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either $L_1$ or $L_2$.

**Apparatus 7(Reciprocating Holder)**

**Apparatus**

- The assembly consist of A set of volumetrically calibrated or tared solution containers made of glass or other suitable inert material, A motor and drive assembly to reciprocate
the system vertically and to index the system horizontally to a different row of vessels automatically if desired, and a set of suitable sample holder (fig 6 & fig 7a-7b). The solution container are partially immersed in a suitable water bath of any convenient size that permits maintaining the temperature, $T$, inside the container at $32 \pm 0.5^\circ$ or within the allowable range.

**Dissolution Medium**

Use the dissolution medium specified in the individual monograph.

**Sample Preparation A (Coated tablet drug delivery system)**

- Attach each system to be tested to a suitable sample holder (e.g., by gluing system edge with 2-cyno acrylate glue onto the end of a plastic rod or by placing the system into a small nylon net bag at the end of a plastic rod or within a metal coil attached to a metal rod).

**Sample Preparation B (Transdermal drug delivery system)**

- Press the system onto a dry, unused piece of cuprophan 4, nylon netting, or equivalent with the adhesive side against the selected substrate, taking care to eliminate air bubbles between the substrate and the release surface. Attach the system to a suitable sized sample holder with a suitable O-ring that the back of the system is adjacent to and centered on the bottom of the disk-shaped sample holder or canted around the circumference of the cylinder-shaped sample holder. Trim the excess substrate with a sharp blade.

**Sample Preparation C (Other drug delivery system)**
Attach each system to be tested to a suitable holder as described in the individual monograph.

**Procedure**

suspend each sample holder from a vertically reciprocating shaker such that each system is continuously immersed in an accurately measured volume of Dissolution Medium within a calibrated container pre-equilibrated to temperature, $T$. Reciprocate at a frequency of about 30 cycles/min. with an amplitude of about 2 cm, or as specified in the individual monograph, for the specified time in the medium specified for each time point. Remove the solution container from the bath, cool to room temperature, and add sufficient solution (i.e., water in most cases) to correct for evaporative losses. Perform the analysis as directed in individual monograph. Repeat the test with additional drug delivery system as required in the individual monograph if the quantities of the active ingredient released from the system conform to Acceptance Table 1 for coated tablet drug delivery systems, to Acceptance Table 4 for Trance dermal drug delivery systems, or as specified in the individual monograph. Continue testing through the three levels unless the results conform at either $L_1$ or $L_2$. 

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ANALYSIS OF HETEROCYCLIC DRUGS

Stainless steel Tubing

Acrylic Rod

Verger Teflon

Parker O-ring

Stainless steel Tubing

0.3175 Diameter - Press fit to head

0.1749 Holes

Stainless steel spring
❖ Reference

1. USP 27, NF 22, Dissolution -2004, 2303.

